16. (Amended) A method of inducing immune tolerance to an antigen, which method comprises administering antigen RNA in an amount effective to elicit immune tolerance against the antigen.

24. (Amended) A pharmaceutical composition comprising an antigen RNA and an pharmaceutical carrier, which pharmaceutical carrier is suitable for *in vivo* delivery to a human.

31. (New) A method for protecting a subject from a cancer which method comprises delivering to epidermal cells of a subject an immunologically effective amount of total tumor cell RNA, wherein the tumor cell is of the type associated with the cancer.

REMARKS

Claims 1-30 are pending in the above-captioned application. With this amendment, claims 16 and 24 are amended and new claim 31 is added. The changes to the claims are fully supported by the specification and no new matter has been introduced. Therefore after entry of this amendment, claims 1-31 will be pending.

Rejections under Section 112, first paragraph

Claims 1-30 are rejected under Section 112, first paragraph, as allegedly not enabled by the specification. The Examiner maintains that applicant has not provided specific guidance for a method of protecting human subjects from cancer, for

treating all types of tumor cells, for treating all pathogens and using all routes of introduction of total tumor cell RNA. Insofar as the claims encompass gene therapy, the Examiner contends that in view of the unpredictable state of the art of gene therapy at the time of the invention, undue experimentation would be required to practice the claimed invention. The Examiner also bases the rejection on the absence of working examples other than experimental fibrosarcoma. Applicant respectfully traverses the rejection.

The specification provides full enabling support for the methods and compositions of claims 1-30. The materials and methods to achieve the claimed invention, considered to be routine experimentation in this field, are fully addressed in the specification, for example, the methods for obtaining total cellular RNA and antigen-specific RNA (pages 14-15);methods for preparing the RNA from tumor cells (page17) ; methods for delivering the RNA into cells (pages 16-17); the conditions which may be treated with the immunogenic compositions of the invention (pages 14-15, 17-18); preparation of RNA vaccines, including the use of suitable adjuvants (pages 19-20);target conditions for immune tolerance and modes of administration to achieve immune tolerance (pages 21-22); and examples using one type of tumor cell model, showing that cellular RNA administered subcutaneously stimulates an immune response and inhibits tumor growth. Applicant describes that the RNA can be successfully transferred into a cell, and applicant describes the diseases for which treatment can be effected. With respect to gene vaccine therapy, the specification clearly describes that delivery of a gene into a cell is within the purview of those skilled in the art. That the technology required to practice the claimed invention was known to those in the art is further demonstrated in many articles which describe the practice of methods related to gene vaccine therapy. The Examiner cites articles (e.g., Eck) that broadly discuss the field of gene therapy, purportedly to show the unpredictability of the art, e.g., in finding appropriate targets, the complexity of cellular uptake of RNA, and the like. Contrary to the Examiner's conclusions, these articles

merely provide a general survey of the field, which does not specifically address why the claimed invention is not enabled with credible scientific evidence. Instead, they establish the existence of myriad solutions to routine problems encountered in implementing gene vaccine therapy. Indeed, Qiu, cited by the Examiner, describes the use of gene guns for administration of nucleic acid for vaccines. In fact the other articles cited in the Office Action, e.g., McCluskie and Eck, provide the guidelines that should be considered in developing gene therapy system and their application to treatment of different diseases. The materials and methods to achieve the claimed invention, considered to be routine experimentation in this field, are also fully addressed in the specification, for example, methods of delivering genes into cells (pages 16-17).

Although one of skill in the art may well have to practice some routine experimentation to achieve the claimed invention depending on the nature of the invention and the state of the art, however this does not constitute undue experimentation. Ex parte Jackson, 217 USPQ 804, 807(Bd PatApp & Inter1982). The Board stated in Jackson that

> A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

(217 USPQ at 807)

Thus, the Examiner has not provided a specific scientific basis for attacking enablement of the claimed invention. Accordingly, the disclosure fully describes the full breadth and scope of the claimed invention. See In re Vaeck, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

The Examiner also bases the rejection on the absence of working examples. However, compliance with the enablement requirement does not turn on whether an example is disclosed. MPEP 2164.02. Applicant is not required to provide working examples in order to have an enabling disclosure, where, as here,

the art has advanced beyond the stage of the art cited by the Examiner.

In view that the applicant has provided sufficient guidance with respect to the direction which one of skill should proceed to practice the invention and in the absence of specific grounds for doubting the applicability of gene therapy for the specifically claimed invention, applicant submits that the specification is fully enabling with respect to claims 1-30.

In addition, applicant provides herein a Declaration under Rule 132 of Richard D. Granstein, the named inventor of the above-captioned application, that demonstrates that the claimed invention, i.e., tolerization, is achieved and therefore fully enabled. The experiment described in the Declaration demonstrates that tolerance is induced by intravenous administration of total cellular RNA from S1509a tumor cells. The results also show that tolerance can be adoptively transferred to naive recipients by transfer by splenic lymphoid cells. Furthermore, antibody and complement-mediated deletion of T cells from the transferred population prevents transfer of tolerance.

In view of the foregoing comments, the evidence presented in the Rule 132 Declaration and the amendment to the claims, applicant submits that the claims are fully enabled by the specification. Applicant respectfully requests that the Section 112, first paragraph rejection of claims 1-30 be withdrawn.

Rejections under Section 112, second paragraph

Claims 1-17, 11, 12, and 16-24 have been rejected under Section 112, second paragraph as indefinite. The amendments to claims 16 and 24 overcome the rejections of these claims. Applicant respectfully traverses the rejection of the remaining claims as vague and indefinite due to incompleteness.

The Examiner asserts that the claims are missing "positive, active steps". The Examiner also asserts that it is unclear "how mere administration relates to" the effects recited in the claims. Applicant submits that the Examiner is

incorrect in requiring further steps in the claims. As the Examiner acknowledges, Applicant is not required to recite all operating details, but it appears that is exactly what the examiner requires. Further, it appears that the Examiner requires that applicant recite all the mechanisms and processes that occur within a recipient of the RNA which result in an immune response, protection or tolerance. These are not required to meet the requirements of the second paragraph of Section 112. Section 112, second paragraph states:

> "The specification shall conclude with one or more claims particularly pointing out and distinctively claiming the subject matter which the applicant regards as his invention."

In the above-captioned application, the invention is that total cellular RNA can generate an immune response or tolerance or protection from pathogens when administered to a recipient. The concept of vaccination and methods of vaccination and stimulating an immune response are not critical limitation to the claims and the specific means by which these steps are taken should not be made limitations in the claims.

The Examiner supports the rejection citing Ex parte Erlich. However in Erlich, the claims merely recited "A process for using" monoclonal antibodies to identify or isolate and purify a protein without reciting any actual steps. In contrast, applicant has positively recited a method step, i.e., that an immune response or tolerance is achieved by administering the RNA to a recipient. How an immune response, tolerance or protection is achieved, or how these are measured, are aspects that are taught throughout the specification and in the examples, however need not be recited in the claims.

The Examiner has also rejected the claims with respect to the term "epidermal cells" . Applicant submits that "epidermal cells" are not synonymous with "dendritic cells" and the term should not be considered to be synonymous with either "dendritic cells" or "professional antigen presenting cells" as used in the

art. An epidermal cell population is a heterogenous population of cells, containing several types of cells including keratinocytes, melanocytes, dendritic cells and Langerhans cells. Typically dendritic cells comprise only about 2% of an epidermal cell population, thus making up only a very small portion of the epidermal cell population. The majority of professional antigen presenting dendritic cells are descended from monocytes and lymphocytes and are typically isolated or purified from blood and lymphoid tissue. The epidermal cells used in the examples of the above-captioned application were enriched for Langerhans cells. However, Langerhans cells, which are a subset of dendritic cells, can be differentiated from dendritic cells morphologically, molecularly and functionally(see, e.g., GJ Clark and DN Hart, "Phenotypic Characteristics of Dendritic Cells" in Dendritic Cells ,555-577, Eds. M. Lotze and AW Thomson, Academic Press, London, 1999, a copy of which is available if required by the Examiner).

In view of the foregoing remarks and amendments, applicant respectfully requests that the Section 112 2nd paragraph rejections be withdrawn.

Rejections under Section 102

Claims 1-3, 5, 8, 9,11, 24 and 28-30 have been rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 5,853,719 (Nair et. al.). Applicant respectfully traverses the rejection.

Nair discloses the use of professional antigen presenting cells pulsed in vitro with tumor cell RNA.

With respect to the method claims, Nair does not disclose the use of epidermal cells to administer the cell RNA. The antigen presenting cells of Nair are purified blood or lymphoid derived dendritic cells. Nair only discloses that these antigen presenting cells were administered for immunization intraperitoneally or that the cells may be administered through infusion techniques. As discussed above, the epidermal cells of the present invention are not dendritic cells and

therefore are not equivalent to the dendritic cells utilized by Nair.

With respect to the composition claims, the claims are directed to pharmaceutical compositions which comprise a pharmaceutical carrier suitable for in vivo delivery to humans. Nair does not disclose pharmaceutical compositions which comprise a pharmaceutical carrier suitable for in vivo delivery to humans. Nair discloses that isolated cells in cell culture media may be administered to mice. However these compositions do not meet the standards required for in vivo delivery into humans required by the present invention. In the specification, applicant sets the standard for pharmaceutical carriers that are suitable for the invention as those carriers "approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans." (see page 20, lines10-13).

In view of the forgoing comments and amendments to the claims, applicant respectfully requests that the Section 102 rejection in view of Nair be withdrawn.

Claims 24 and 29 have been rejected under 35 U.S.C. §102(a) as anticipated by Zhang et al. Applicant herewith submits a Rule 131 Declaration of Richard D. Granstein, the named inventor of the above-captioned application. The Rule 131 Declaration provides evidence that applicant invented the claimed subject matter prior to the May 1, 1999 publication date of Zhang. The evidence presented in the Declaration provides a description of experiments that demonstrate conception and reduction to practice before the May1, 1999 date that applicant successfully immunized mice using tumor total cellular RNA against the formation of tumors when challenged with tumor cells. Applicant respectfully submits that the Zhang article is removed as prior art and the rejection under Section 102 in view of Zhang should be withdrawn.

Claims 24 and 30 have been rejected as anticipated by Qiu et al. Applicant respectfully traverses the rejection.

Qui et al. disclose RNA transcripted from three reporter genes, gene gun delivery of the mRNA to epidermis, and production of antibodies against the expressed product. Applicant notes that the Examiner incorrectly states that Qui teaches gene gun delivery of tumor cell mRNA. However, Qui does not teach delivery to the epidermis of mRNA encoding a melanoma antigen; rather only firefly luciferase, human growth hormone and human alpha trypsin were employed. A tumor cell line was used as a target cell for bombardment of the mRNA.

Qui does not disclose the claimed invention because the compositions of Qui do not meet the standards required for in vivo delivery into humans required by the present invention. As discussed above, applicant sets the standard in the specification for pharmaceutical carriers that are suitable for the invention as those carriers approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans." (see page 20, lines10-13). Instead, Qui utilized RNA/gold particle complexes.

In view of the foregoing comments and amendments to the claims, applicant respectfully requests that the Section 102 rejection in view of Qui be withdrawn.

Rejections under Section 103

Claims 1-3, 5, 7, 8, 9,11, 12, 24, 28 and 30 have been rejected under 35 U.S.C. §103(a) as unpatentable over Zhang et al taken with Nair et al. As discussed above, Zhang has been removed as prior art, therefore the rejection cannot stand. Applicant respectfully requests that the rejection be withdrawn.

Claims 1-5, 7, 8, 9,11, 24, 28 and 29 have been rejected under 35 U.S.C. §103(a) as unpatentable over Qui et al taken with Nair et al. Applicant respectfully traverses the rejection.

Qui et al.may be distinguished from the present invention in that the

production of antibodies against the expressed product does not establish that a protective immune response will be generated. Qui et al. discloses the use of a gene gun to introduce RNA transcripts of three separate reporter genes resulting in expression of protein in vivo after bombardments to rat liver tissue, mouse liver tissue and mouse epidermis. Protein expression could be subsequently detected in mouse epidermal tissues. Additionally, the use of the gene gun to introduce mRNA for human alpha 1 antitrypsin into mouse epidermis resulted in a positive antibody response against that protein. However, the production of antibodies against a protein encoded for by a single mRNA does not establish that a protective immune response would be generated by this technique. Neither would one of skill in the art, in view of this teaching, reasonably expect that a protective immune response would be generated by total cellular mRNA or total cellular RNA. As mentioned above, Qui et al. does not use tumor cell mRNA. Thus Qui does not teach or suggest that a protective immune response would be generated by this technique against a tumor.

With respect to Nair, applicant submits that it is not obvious that the exposure of a heterogenous population of epidermal cells to RNA would yield the same effect as using a purified population of blood or lymphoid derived dendritic cells. Further, Nair does not teach or suggest the use of epidermal cells or subcutaneous administration of RNA, thus with respect to methods of administration, thus one of skill in the art would not have a reasonable expectation of success that vaccination subcutaneously, i.e., via epidermal cells, would produce the same result as vaccination intraperitoneally or through infusion, the only methods of administration taught or suggested by Nair.

In order to support a case for obviousness, the references must provide a reasonable expectation of success. Thus, even if the references made it "obvious to try "to evaluate total cellular mRNA or total cellular RNA, or subcutaneous administration, they by no means provide the requisite reasonable

expectation of success, or any expectation of success, of practicing the claimed invention.

One of skill would not be motivated to combine Nair with Qui et al. Qui et al. does not teach or suggest the delivery of tumor mRNA; this suggestion only comes from applicant's invention. As the Examiner acknowledges, Qui et al. does not use total pathogen RNA or total mRNA; this suggestion also only comes from applicant's invention. However, this is not a proper basis to support a rejection for obviousness. In order to support a rejection for obviousness, the suggestion to combine the references must come from the references themselves, not from the teachings of the applicant. In re Fine, 5USPQ2d, 1596 (Fed.Cir. 1988). In view of the foregoing remarks , applicant submits that obviousness has not been established and that the rejection cannot stand. Applicant respectfully requests that the Section 103 rejection of the claims over Qui et al. in view of Nair be withdrawn.

CONCLUSION

In view of the foregoing, applicant respectfully submits that the claims are in form for allowance. Allowance of the application is earnestly solicited.

Respectfully submitted,

Raina Semionow
Reg. No. 39,022
Attorney for Applicant

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700
::ODMA\WORLDOX\M:\2650\1F966US2\RXS0940.WPD

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PATENT TRADEMARK OFFICE

Docket No: 2650/1F966

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard D. Granstein

Serial No.: 09/679,776 Art Unit: 1632

Confirmation No.:

Filed: October 5, 2000 Examiner: J. Li

For: PROTECTIVE IMMUNITY OR IMMUNOLOGICAL TOLERANCE INDUCED WITH RNA, PARTICULARLY TOTAL CELLULAR RNA

MARKED UP CLAIMS

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

September 20, 2001

Sir:

This is in connection with the response to the Office Action dated June 20, 2001 received in the above-captioned application. Please amend the claims as follows:

16. (Amended) A method of inducing immune tolerance to an antigen, which method comprises administering antigen RNA in an amount effective to elicit immune tolerance against the antigen [through a tolerization route of administration].

24. (Amended) A pharmaceutical composition comprising an antigen RNA and an pharmaceutical carrier, which pharmaceutical carrier is suitable for in vivo delivery to a human.

Respectfully submitted,

Raina Semionow

Raina Semionow
Reg. No. 39,022
Attorney for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

::ODMA\WORLDOX\M:\2650\1F966\RXS0943.WPD